Published in final edited form as:
Psychosom Med. 2012 July ; 74(6): 642–647. doi:10.1097/PSY.0b013e3182590904.

Predictors of Cancer-related Pain Improvement Over Time

Hsiao-Lan Wang, PhD, RN, CMSRN, HFS, **Kurt Kroenke, MD**, **Jingwei Wu, MS**, **Wanzhu Tu, PhD**, **Dale Theobald, MD, PhD**, and **Susan M. Rawl, PhD, RN, FAAN**
College of Nursing, University of South Florida, Tampa (H.W.); Department of Medicine, Indiana University, Indianapolis (K.K., J.W., W.T.); Regenstrief Institute, Inc., Indianapolis (K.K., W.T.); Center for Implementing Evidence-based Practice, Richard L. Roudebush VA Medical Center, Indianapolis (K.K.); Community Cancer Care, Indianapolis (D.T.); Community Health Network, Indianapolis (D.T.); and School of Nursing, Indiana University (S.M.R.)

Abstract

Objective—To determine the predictors of pain improvement among patients being treated for cancer-related pain over 12 months.

Methods—A secondary analysis of the Indiana Cancer Pain and Depression (INCPAD) trial was performed. Patients participating in this telephone care management pain and depression intervention trial (N=274, mean age=58.1±10.5 years, 66.1% women) were interviewed at baseline, and 1, 3, 6, and 12 months. Pain improvement outcomes included both a continuous measure (Brief Pain Inventory score) and a categorical measure (pain improved vs. pain not improved). Predictor variables included change in depression, age, gender, race, marital status, socioeconomic disadvantage, medical comorbidity, type of cancer, and phase of cancer. Multivariable repeated measures were conducted adjusting for intervention group assignment, baseline pain severity, and time in months since baseline assessment.

Results—Factors predicting both continuous and categorical pain improvement included participating in the intervention group (beta=−.92, p<.001; *OR*=2.53, CI=1.65–3.89), greater improvement in depression (beta=−.31, p=.003; *OR*=1.84, CI=1.35–2.51), higher socioeconomic status (Socioeconomic Disadvantage Index; beta=.25, p=.034; *OR*=.73, CI=.56–.94), and fewer comorbid conditions (beta=.20, p=.002; *OR*=.84, CI=.73–.96). Conversely, patients with more severe pain at baseline or with recurrent or progressive cancer were less likely to experience continuous or categorical pain improvement, respectively.

Conclusions—Effective management of depression and comorbid conditions along with improvement of social services could be critical components of a comprehensive pain management plan. Also, patients with more severe pain or with recurrent or progressive cancers may require closer monitoring and adequate treatment of pain.

Clinical Trial Registration Number—NCT00313573

Keywords

Cancer-related pain; pain improvement; predictors; longitudinal study

Corresponding author: Hsiao-Lan Wang, PhD, RN, CMSRN, HFS, 12901 Bruce B. Downs Blvd., MDC22, Tampa, FL 33612, Phone: 317-658-2275, hwang5@health.usf.edu.

None of the other authors have conflicts to declare.

1. Introduction

It is estimated that about 1.6 million people were diagnosed with cancer in 2011 (1). For some people, pain is the first symptom of cancer (2). Cancer-related pain can occur at any time during the course of the disease (3) and may be caused by tumor infiltration/involvement, diagnostic or therapeutic procedures, or cancer treatment (3, 4).

Prevalence of cancer-related pain varies based on cancer type, cancer trajectory, and demographics. Up to 64% of patients experience cancer-related pain (5) and 82% have their pain undertreated by analgesics (6). Undertreated pain can lead to lower quality of life (7, 8), negative emotional states (8), interference with daily activities (9, 10), disability (11, 12), and delay/disruption of cancer treatment (13, 14), all of which reduce the effectiveness of the cancer treatment (15) and survival rates (3).

To avoid the consequences of undertreated pain, effective pain management is essential. In addition to analgesics, other factors that influence pain include age (14), gender (14, 16–19), race (14, 17, 20), socioeconomic status (6, 14, 21), comorbid conditions (19), type of cancer (3, 22), and phase of cancer (5, 13). The complex interplay of these factors could explain why some patients experience pain improvement while others report persistent pain despite analgesic treatment. However, the majority of previous studies investigating factors that influence pain have been cross-sectional in design.

The relationship between pain and depression is well known (23–32). Again, most of the studies have been cross-sectional (23–26, 31, 32), so the temporal relationship is less well documented. A small number of longitudinal studies have found current depression or change in depression over time predicted subsequent pain among older adults in communities or among patients from primary care clinics (27, 28, 30). But none of these studies was conducted among cancer populations.

The Indiana Cancer Pain and Depression (INCPAD) study, a randomized clinical trial implemented with patients who had different types and phases of cancer, tested a 12-month telephone care management intervention designed to decrease pain and/or depression (33, 34). In the INCPAD trial, we found moderate pain improvement in the intervention group compared to the usual-care group among patients being treated for cancer-related pain and/or depression ($p < .001$) (34). Because the INCPAD study included multiple data collection time points, it lends itself to repeated measures analysis, which is a particularly strong method for studying longitudinal relationships between pain and other variables over time (35). Therefore, we conducted a secondary analysis to determine which factors, besides the intervention, predicted pain improvement. Specifically, our research question was: What are the predictors of pain improvement among patients being treated for cancer-related pain over 12 months?

2. Method

2.1. Sample and Setting

The design and baseline participant characteristics in the INCPAD study have been published elsewhere (12, 33, 34). Patients with cancer-related pain and/or depression were recruited from 16 urban and rural outpatient oncology clinics. Potential participants were patients who had moderately severe cancer-related pain (a Brief Pain Inventory [BPI] worst pain severity score ≥ 6), or depression (a Patient Health Questionnaire 9-item depression scale [PHQ-9] score ≥ 10, with depressed mood and/or anhedonia) (24, 36–38). Cancer-related pain had to be in the region of the primary tumor or cancer metastases and/or present after the onset of the cancer treatment. Patients with cancer-related pain had to have tried at

least one analgesic but still be experiencing pain. The study excluded those who did not speak English, had moderately severe cognitive impairment as defined by a 6-item cognitive screener (39), had schizophrenia or other psychoses, had a disability claim currently being adjudicated for pain, were pregnant, were in hospice care, or had pre-existing pain conditions unrelated to cancer.

A total of 405 participants with depression, cancer-related pain, or both were enrolled in the INCPAD trial. For this secondary analysis, data from 274 participants who had cancer-related pain (with or without depression) were analyzed: 137 in the intervention group and 137 in the usual care group. These 274 participants were enrolled from a group of 444 patients who met all entry criteria for cancer-related pain, thus yielding an enrollment rate of 62% of potentially eligible patients. The intervention group received centralized telephone care management (telecare) focusing on optimizing medications to treat their cancer-related pain and/or depression, while the usual-care group received care by their oncologists without attempts by study personnel to influence their pain and/or depression treatment unless a psychiatric emergency arose. Details of the telecare intervention have been described previously (33). Our analysis combined the intervention and control groups to examine the factors that influence pain management after controlling for treatment arm assignment.

2.2. Data Collection

Research assistants who conducted the phone interviews to collect data at baseline (T0), 1 month (T1), 3 months (T3), 6 months (T6), and 12 months (T12) were blinded to group assignment. Medical record reviews from the oncology practice were performed during the study. The study was approved by the Indiana University and Community Hospitals' institutional review boards.

2.3. Measures

2.3.1 Outcome Variables—Pain improvement was measured by the Brief Pain Inventory (BPI) severity scale and a single item assessing pain improvement, Pain Global Rating of Improvement (PGRI). The BPI severity scale asks participants to rate their pain at its worst, its least, and on average in the previous week, as well as their current pain on a 0 (*no pain*) to 10 (*pain as bad as you can imagine*) point scale (36, 40). The mean of the 4 items was determined, with higher scores reflecting more severe pain. The BPI had adequate internal reliability (Cronbach's $\alpha = .79$) in the INCPAD study (33). The PGRI evaluates the participants' overall impression of the change in their pain since study enrollment, asking whether their pain was *worse*, *about the same*, or *better* (33, 41). The PGRI has been found to be more sensitive to changes in pain and better correlated with patient satisfaction than the visual analog scale (42). Consensus guidelines for outcome assessment of pain treatments in clinical trials recommend both a continuous measure of pain severity as well as a patient-rated assessment of global improvement since the two measures capture somewhat different, but complementary, dimensions of pain improvement (43).

2.3.2 Predictor Variables—Depression was measured using the Hopkins Symptom Checklist 20-item depression scale (HSCL-20) (44). The 20 items are questions about how much participants had been distressed by different symptoms of depression during the previous 4 weeks on a 0 (*not at all*) to 5 (*extremely*) scale. The mean of these items is calculated, yielding a range on a scale of 0 to 5, with higher scores reflecting more severe depression. The HSCL-20 had good internal reliability ($\alpha = .79$) in INCPAD (33).

Other variables examined as potential predictors included demographics (age, gender, race, marital status, education, job status, and income) and baseline clinical factors (medical comorbidity, type of cancer, and phase of cancer). The Socioeconomic Disadvantage (SED)

Index is a composite score combining the three inter-related variables of education, income, and employment status into a single variable; the SED Index is calculated by assigning 1 point each for low education ("less than high school"), unemployment ("unable to work due to health or disability"), and low income ("not enough to make ends meet") (12). Medical comorbidity was measured using a checklist of eight diseases that has been shown to predict health care utilization and mortality in medical populations (45). Type of cancer and phase of cancer were obtained from participants' medical records. Phase of cancer was categorized as newly diagnosed, maintenance/disease-free, or recurrent/progressive.

2.4. Statistical Analysis

As noted, our research question was: What are the predictors of pain improvement among patients being treated for cancer-related pain over 12 months? The two pain improvement outcome variables were BPI severity and PGRI at T1, T3, T6, and T12. The BPI severity score was a continuous variable. PGRI was recoded as a binary variable: 1 as "pain improved" for participants who answered *better* on the PGRI, and 0 as "pain not improved" for participants who answered *worse* or *about the same* on the PGRI.

Predictor variables included age, gender, race, marital status, SED Index, medical comorbidity, type of cancer, and phase of cancer. We used a sophisticated method to examine the temporal influence of depression improvement on the sequent pain outcome (28). Figure 1 diagrams the repeated measures modeling for the predictive relationship: preceding improvement in depression predicting subsequent pain improvement over 12 months. Specifically, we modeled the relationship of HSCL-20 change scores between baseline and 1 month (T1–T0) to BPI or PGRI at T1; between 1 month and 3 months (T1–T3) to BPI or PGRI at T3; between 3 months and 6 months (T3–T6) to BPI or PGRI at T6; and between 6 months and 12 months (T6–T12) to BPI or PGRI at T12. Data from study participants at each time point were analyzed by the generalized linear mixed effects models for repeated measures (MMRM) to elucidate the relationship between depression change and pain, with the former as a predictor and latter as the outcome. In this analysis, random subject effect was incorporated into the model to accommodate the potential correlation among the repeatedly measured outcomes within subjects. We developed a full model by adjusting for group assignment, baseline BPI severity, and time in months since baseline assessment. The analyses were performed using PRO MIXED of SAS Version 9.1 (SAS Institute, Cary, North Carolina). p values less than .05 were considered statistically significant.

3. Results

3.1. Patient characteristics

The baseline characteristics of the participants are shown in Table 1. Two-thirds of the participants were female, 77% were white, and 65% had both cancer-related pain and depression upon enrollment in the study. Their mean age was 58 years, with a range from 23 to 85 years old. At baseline, participants reported moderate pain intensity on the BPI scale. There was a wide distribution of types and phases of cancer, a consequence of screening all patients attending the participating oncology practices. Previous analyses showed that, as expected from the randomized allocation design of the trial, the intervention and usual care groups were similar in all baseline characteristics (34). Compared to the usual care group, patients in the telecare intervention group had significantly greater pain improvement (effect size of .46 and .39 at 6 and 12 months, $p < .001$) and depression improvement (effect size of .45 and .41 at 6 and 12 months, $p < .001$) (34).

3.2. Predictors of Pain Improvement

Table 2 summarizes the results from the multivariable MMRM for the two outcome variables. As expected, being in the intervention group and having lower baseline pain severity were strongly associated with better pain outcomes over 12 months. Also, the time in months since baseline assessment was significantly associated with reduced BPI scores. Other independent predictors of improvement in BPI severity over 12 months were better socioeconomic status (i.e., a lower SED Index score) and less medical comorbidity. Importantly, improvement in depression was the strongest predictor ($t = -2.97$, $p = .003$). A preceding 1-point improvement in HSCL-20 depression severity predicted subsequent reduction in BPI pain severity of .31 points.

Similar to the BPI severity model, independent predictors of Pain Global Rating of Improvement (PGRI) over 12 months included being in the intervention group, time in months since enrollment, better socioeconomic status, and less medical comorbidity. Again, improvement in depression was the strongest predictor ($OR = 1.84$ for each 1-point improvement in HSCL-20 depression score, 95% CI = 1.35–2.51). An additional predictor was cancer phase: participants whose cancer was newly-diagnosed were more than twice as likely to experience pain improvement compared with those with recurrent or progressive cancer. Although the association between phase of cancer and BPI severity did not reach significance, there was a trend towards an association ($p = .07$).

4. Discussion

Our study makes several important contributions to the literature about the relationship between pain and depression. First, we used a sophisticated analytical strategy which strengthens conclusion regarding the predictive relationships between depression and pain. Second, this is the first longitudinal study examining the depression-pain relationship in cancer populations. Third, we found that preceding improvement in depression is a strong predictor of subsequent pain.

Our analytical strategy is particularly strong. Conceptually, the INCPAD study is a clinical trial treating both cancer-related pain and depression (33). Depression (HSCL-20 score) was a dynamic variable that changed in both the intervention and usual care groups over the 12-month study period (34). Because of the longitudinal nature of the INCPAD study, we were able to assess whether change in depression during *preceding* time intervals predicted reduced pain severity and pain improvement at *subsequent* time points repeatedly over a 12-month period. In addition, the multivariate MMRM applied in our study allows repeated measures from the same subject to share a common random effect (46, 47). This analysis helps to establish within-subject associations between pain and depression. Therefore, the MMRM method may provide a better fit model than the population averaged model, such as generalized estimating equations (GEE) analysis used to assess group average associations between pain and depression in previous longitudinal studies (27, 30). Our use of MMRM analysis is a sophisticated approach to examine the temporal relationship between depression and pain but it has not been applied among cancer patients (26, 28). Furthermore, we adjusted for multiple important confounders: intervention assignment, baseline pain severity, and the passage of time. Even controlling for these factors, the predictors identified from our analysis still showed significant effects on pain improvement.

The important finding in our study is the beneficial association between improvement in depression and pain outcomes in cancer patients. This result is not only consistent with previous studies that have suggested a predictive relationship from depression to pain in geriatric and primary care populations (27–30), but also supports a similar relationship in the cancer population. Clinically, it is suggested that effectively treating comorbid depression in

patients with cancer-related pain may be an important adjunct to optimizing analgesic therapy and other pain-specific treatments. This finding from our study highlights the potential importance of screening for, monitoring, and treating both symptoms concurrently in cancer patients.

Socioeconomic disadvantage and pain risk have been positively linked in patients with musculoskeletal, sciatica, ulcer, and neuropathic pain (21). Consistent with this, our analysis showed that participants with better socioeconomic status were more likely to experience improvement in cancer-related pain. Other studies have found that patients with lower incomes and educational attainment had a high risk of undertreated cancer-related pain (6, 13). Socioeconomically disadvantaged patients may be more likely to have negative pain beliefs, possess little or no health insurance, have less social support, and use passive coping styles, all of which may contribute to uncontrolled chronic cancer-related pain (6). To cancer patients who are disadvantaged socioeconomically, clear and appropriate pain education, additional care management, and supportive social services may be necessary when a pain management program is implemented. Referrals to social workers and public welfare agencies as well as resources for cancer survivors may be important to consider for this vulnerable subgroup of the population.

Patients with a greater number of comorbid medical conditions were less likely to report improvement in their cancer-related pain in our study. The National Health Interview Survey has shown that a higher number of comorbid conditions were significantly associated with poor health status and disability among cancer patients (48). From our findings, it is suggested that cancer patients with pre-existing chronic diseases are more likely to develop persistent cancer-related pain, which could contribute to poor health status and disability (8, 11, 12). Effective management of pre-existing chronic conditions may further optimize treatment outcomes in patients with cancer-related pain.

Not surprisingly, we found that patients with recurrent or progressive cancer had worse pain outcomes over 12 months than those who were newly-diagnosed. The most difficult to treat cancer-related pain is the pain caused by tumor involvement, where tumor mass has invaded surrounding or distant structures (3, 15). Therefore, patients with cancer-related pain in the recurrent or progressive phase of their illness may require more frequent monitoring of their pain and more aggressive pain treatment. In contrast, a recent diagnosis of cancer seemed to be an independent predictor of better pain outcomes. It may be that dysphoric mood is reactive and time limited among a subset of newly- diagnosed cancer patients. Likewise, pain may also be more transient in some of these patients, being a consequence of surgery, radiation, or chemotherapeutic neuropathy, and may subsequently resolve following completion of treatment. In such cases, pain may simply lag behind the resolution of depressed mood rather than being causally related.

Disparities of pain management have been observed in several populations including older age, female gender, and minority race (14). Studies found older age was associated with inadequate pain management among patients in the nursing home or hospital (14, 49). Our study suggested that age is not related to pain improvement among those from the outpatient oncology clinic. For gender, one study found that more female patients had undertreated pain than their counterparts (14). Women tended to be careless at times about taking pain medication and were more likely to stop taking the pain medication when they felt better (50). We did not see a relationship between gender and pain improvement in our study, a finding similar to that of other studies conducted in cancer patients (51, 52). Finally, some earlier studies indicated that ethnic minority patients reported undertreated pain because those patients did not receive an adequate amount of analgesics (14, 18, 53). In our study, race was not associated with either pain improvement outcome. However, we could not

ascertain whether the ethnic minority participants in our study had received an adequate amount of analgesics.

Our study has several limitations. First, the INCPAD enrollment criteria created a study sample enriched with depressed patients with pain. These patients may not be representative of cancer patients in general, even though their demographic and disease characteristics are similar. Whether the finding demonstrated in our sample would be similar in cancer populations with lesser degrees of pain or depression should be further explored. Second, it is possible that our finding of improvement in depression over a preceding time interval predicting subsequent pain might be partly explained by pain improvement in the preceding interval. Therefore, an alternative explanation of our data is that reduced pain at a particular time point represented preceding pain improvement, which may have influenced improvement in depression. Although our repeated measures analytical strategy modeling improvement in depression over multiple time intervals to predict end-of-interval pain status at multiple time points strengthens the case for a temporal linkage from improvement in depression to lower pain, it does not establish this reciprocal relationship with complete certainty. Nonetheless, our findings are consistent with results from longitudinal studies in noncancer populations that have shown that change in depression predicts pain outcomes (28).

Our findings from this 12-month longitudinal study of pain outcomes in patients with cancer-related pain suggest that several factors may be important to consider in developing a more comprehensive approach to pain management. For example, proactively managing depression and other comorbid conditions, as well as enhancing sufficient social support, might be useful adjuncts to pain treatment, particularly in patients whose pain is not responding to standard analgesic management. Also, patients with more severe pain at baseline as well as those with recurrent or progressive cancers may benefit from closer monitoring of their pain and, in some cases, more aggressive pain treatment. Gaining an understanding of some of the demographic and clinical factors that influence pain outcomes might enable clinicians to tailor and augment treatment in selected patients with more persistent or refractory cancer-related pain.

Acknowledgments

Funding: This study was supported by a grant from the National Cancer Institute to Dr. Kroenke (R01 CA-115369). Dr. Wang was supported by an institutional training grant from the National Institute of Nursing Research (T32 NR007066). The content of the manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institute of Nursing Research. Dr. Kroenke has received honoraria and consulting fees from Eli Lilly and Forest Pharmaceuticals.

Glossary

BPI	Brief Pain Inventory
HSCL-20	Hopkins Symptom Checklist 20-item depression scale
INCPAD	Indiana Cancer Pain and Depression
MMRM	Mixed Effects Models for Repeated Measures
PGRI	Pain Global Rating of Improvement
PHQ-9	Patient Health Questionnaire 9-item depression scale
SED	Socioeconomic Disadvantage
T0	baseline data collection

T1	1-month data collection
T3	3-month data collection
T6	6-month data collection
T12	12-month data collection
Telecare	centralized telephone care management

References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011; 61:212–36. [PubMed: 21685461]
2. Learn about Cancer: Find information and resources for a specific cancer topic. American Cancer Society; 2010. Sign and Symptom of Cancer. Availible at: http://www.cancer.org/Cancer/CancerBasics/signs-and-symptoms-of-cancer
3. Mantyh PW. Cancer pain and its impact on diagnosis, survival and quality of life. Nat Rev Neurosci. 2006; 7:797–809. [PubMed: 16988655]
4. McGuire DB. Occurrence of cancer pain. J Natl Cancer Inst Monogr. 2004:51–6. [PubMed: 15263041]
5. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007; 18:1437–49. [PubMed: 17355955]
6. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. Ann Oncol. 2008; 19:1985–91. [PubMed: 18632721]
7. Holen JC, Lydersen S, Klepstad P, Loge JH, Kaasa S. The Brief Pain Inventory: pain's interference with functions is different in cancer pain compared with noncancer chronic pain. Clin J Pain. 2008; 24:219–25. [PubMed: 18287827]
8. Tavoli A, Montazeri A, Roshan R, Tavoli Z, Melyani M. Depression and quality of life in cancer patients with and without pain: the role of pain beliefs. BMC Cancer. 2008; 8:177. [PubMed: 18570676]
9. Lin CC, Lai YL, Ward SE. Effect of cancer pain on performance status, mood states, and level of hope among Taiwanese cancer patients. J Pain Symptom Manage. 2003; 25:29–37. [PubMed: 12565186]
10. Wells N, Murphy B, Wujcik D, Johnson R. Pain-related distress and interference with daily life of ambulatory patients with cancer with pain. Oncol Nurs Forum. 2003; 30:977–86. [PubMed: 14603355]
11. Wang HL, Kroenke K, Wu J, Tu W, Theobald D, Rawl SM. Cancer-related pain and disability: A Longitudinal study. J Pain Symptom Manage. 2011
12. Kroenke K, Theobald D, Wu J, Loza JK, Carpenter JS, Tu W. The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. J Pain Symptom Manage. 2010; 40:327–41. [PubMed: 20580201]
13. Fairchild A. Under-treatment of cancer pain. Curr Opin Support Palliat Care. 2010; 4:11–5. [PubMed: 20040878]
14. McNeill JA, Sherwood GD, Starck PL. The hidden error of mismanaged pain: a systems approach. J Pain Symptom Manage. 2004; 28:47–58. [PubMed: 15223084]
15. McCloskey SA, Jaggernauth W, Rigual NR, Hicks WL Jr, Popat SR, Sullivan M, Mashtare TL Jr, Khan MK, Loree TR, Singh AK. Radiation treatment interruptions greater than one week and low hemoglobin levels (12 g/dL) are predictors of local regional failure after definitive concurrent chemotherapy and intensity-modulated radiation therapy for squamous cell carcinoma of the head and neck. Am J Clin Oncol. 2009; 32:587–91. [PubMed: 19581794]
16. Cairns BE, Gazerani P. Sex-related differences in pain. Maturitas. 2009; 63:292–6. [PubMed: 19595525]

17. Im EO, Chee W, Guevara E, Liu Y, Lim HJ, Tsai HM, Clark M, Bender M, Suk Kim K, Hee Kim Y, Shin H. Gender and ethnic differences in cancer pain experience: a multiethnic survey in the United States. Nurs Res. 2007; 56:296–306. [PubMed: 17846550]
18. Jones A, Zachariae R, Arendt-Nielsen L. Dispositional anxiety and the experience of pain: gender-specific effects. Eur J Pain. 2003; 7:387–95. [PubMed: 12935790]
19. Valeberg BT, Miaskowski C, Hanestad BR, Bjordal K, Paul S, Rustoen T. Demographic, clinical, and pain characteristics are associated with average pain severity groups in a sample of oncology outpatients. J Pain. 2008; 9:873–82. [PubMed: 18571988]
20. Stephenson N, Dalton JA, Carlson J, Youngblood R, Bailey D. Racial and ethnic disparities in cancer pain management. J Natl Black Nurses Assoc. 2009; 20:11–8. [PubMed: 19691179]
21. Poleshuck EL, Green CR. Socioeconomic disadvantage and pain. Pain. 2008; 136:235–8. [PubMed: 18440703]
22. Burton AW, Fanciullo GJ, Beasley RD, Fisch MJ. Chronic pain in the cancer survivor: a new frontier. Pain Med. 2007; 8:189–98. [PubMed: 17305690]
23. Gureje O, Simon GE, Von Korff M. A cross-national study of the course of persistent pain in primary care. Pain. 2001; 92:195–200. [PubMed: 11323140]
24. Williams LS, Jones WJ, Shen J, Robinson RL, Kroenke K. Outcomes of newly referred neurology outpatients with depression and pain. Neurology. 2004; 63:674–7. [PubMed: 15326241]
25. Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. Psychosom Med. 2004; 66:17–22. [PubMed: 14747633]
26. Laird BJ, Boyd AC, Colvin LA, Fallon MT. Are cancer pain and depression interdependent? A systematic review. Psychooncology. 2009; 18:459–64. [PubMed: 18942659]
27. Geerlings SW, Twisk JW, Beekman AT, Deeg DJ, van Tilburg W. Longitudinal relationship between pain and depression in older adults: sex, age and physical disability. Soc Psychiatry Psychiatr Epidemiol. 2002; 37:23–30. [PubMed: 11926200]
28. Kroenke K, Wu J, Baier ML, Krebs EE, Damush TM, Tu W. Reciprocal relationship between pain and depression: A 12-month longitudinal analysis in primary care. J Pain. 2011; 12:964–973. [PubMed: 21680251]
29. Hawker GA, Gignac MA, Badley E, Davis AM, French MR, Li Y, Perruccio AV, Power JD, Sale J, Lou W. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. Arthritis Care Res (Hoboken). 2010
30. Hurwitz EL, Morgenstern H, Yu F. Cross-sectional and longitudinal associations of low-back pain and related disability with psychological distress among patients enrolled in the UCLA Low-Back Pain Study. J Clin Epidemiol. 2003; 56:463–71. [PubMed: 12812821]
31. Chou KL. Reciprocal relationship between pain and depression in older adults: evidence from the English Longitudinal Study of Ageing. J Affect Disord. 2007; 102:115–23. [PubMed: 17240455]
32. Meyer T, Cooper J, Raspe H. Disabling low back pain and depressive symptoms in the community-dwelling elderly: a prospective study. Spine (Phila Pa 1976). 2007; 32:2380–6. [PubMed: 17906583]
33. Kroenke K, Theobald D, Norton K, Sanders R, Schlundt S, McCalley S, Harvey P, Iseminger K, Morrison G, Carpenter JS, Stubbs D, Jacks R, Carney-Doebbeling C, Wu J, Tu W. The Indiana Cancer Pain and Depression (INCPAD) trial Design of a telecare management intervention for cancer-related symptoms and baseline characteristics of study participants. Gen Hosp Psychiatry. 2009; 31:240–53. [PubMed: 19410103]
34. Kroenke K, Theobald D, Wu J, Norton K, Morrison G, Carpenter J, Tu W. Effect of telecare management on pain and depression in patients with cancer: a randomized trial. JAMA. 2010; 304:163–71. [PubMed: 20628129]
35. Benecluk J, George S. Evaluation: Reciprocal relationship between pain and depression: A 12-month longitudinal analysis in primary care. Faculty of 1000: Post-Publicatoin Peer Review. 2011
36. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med. 1994; 330:592–6. [PubMed: 7508092]

37. Cleeland, CS. Pain Assessment in cancer. In: Osoba, D., editor. Effect of cancer on quality of life. Boca Raton, FL: CRC Press; 1991.
38. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med. 2001; 16:606–13. [PubMed: 11556941]
39. Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC. Six-item screener to identify cognitive impairment among potential subjects for clinical research. Med Care. 2002; 40:771–81. [PubMed: 12218768]
40. Cleeland, CS. The Brief Pain Inventory user guide. Houston, Texas: The University of Texas MD Anderson Cancer Center; 2009. Avialible at http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/symptom-research-brief-pain-inventory-user-s-guide.html
41. Krebs EE, Lorenz KA, Bair MJ, Damush TM, Wu J, Sutherland JM, Asch SM, Kroenke K. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. J Gen Intern Med. 2009; 24:733–8. [PubMed: 19418100]
42. Fischer D, Stewart AL, Bloch DA, Lorig K, Laurent D, Holman H. Capturing the patient's view of change as a clinical outcome measure. JAMA. 1999; 282:1157–62. [PubMed: 10501119]
43. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008; 9:105–21. [PubMed: 18055266]
44. Williams JW Jr, Stellato CP, Cornell J, Barrett JE. The 13- and 20-item Hopkins Symptom Checklist Depression Scale: Psychometric properties in primary care patients with minor depression or dysthymia. Int J Psychiatry Med. 2004; 34:37–50. [PubMed: 15242140]
45. Perkins AJ, Kroenke K, Unutzer J, Katon W, Williams JW, Hope C, Callahan CM. Common comorbidity scales were similar in their ability to predict health care costs and mortality. J Clin Epidemiol. 2004; 57:1040–8. [PubMed: 15528055]
46. Lee Y, Nelder JA. Conditional and marginal models: Another view. Statistical Science. 2004; 21:219–38.
47. Lindsey JK, Lambert P. On the appropriateness of marginal models for repeated measurements in clinical trials. Stat Med. 1998; 17:447–69. [PubMed: 9496722]
48. Hewitt M, Rowland JH, Yancik R. Cancer survivors in the United States: Age, health, and disability. J Gerontol A Biol Sci Med Sci. 2003; 58:82–91. [PubMed: 12560417]
49. Bernabei R, Gambassi G, Lapane K, Landi F, Gatsonis C, Dunlop R, Lipsitz L, Steel K, Mor V. Management of pain in elderly patients with cancer. SAGE Study Group. Systematic Assessment of Geriatric Drug Use via Epidemiology. JAMA. 1998; 279:1877–82. [PubMed: 9634258]
50. Valeberg BT, Miaskowski C, Hanestad BR, Bjordal K, Moum T, Rustoen T. Prevalence rates for and predictors of self-reported adherence of oncology outpatients with analgesic medications. Clin J Pain. 2008; 24:627–36. [PubMed: 18716502]
51. Thomason TE, McCune JS, Bernard SA, Winer EP, Tremont S, Lindley CM. Cancer pain survey: patient-centered issues in control. J Pain Symptom Manage. 1998; 15:275–84. [PubMed: 9654832]
52. Zeppetella G. How do terminally ill patients at home take their medication? Palliat Med. 1999; 13:469–75. [PubMed: 10715753]
53. Anderson KO, Mendoza TR, Valero V, Richman SP, Russell C, Hurley J, DeLeon C, Washington P, Palos G, Payne R, Cleeland CS. Minority cancer patients and their providers: pain management attitudes and practice. Cancer. 2000; 88:1929–38. [PubMed: 10760771]

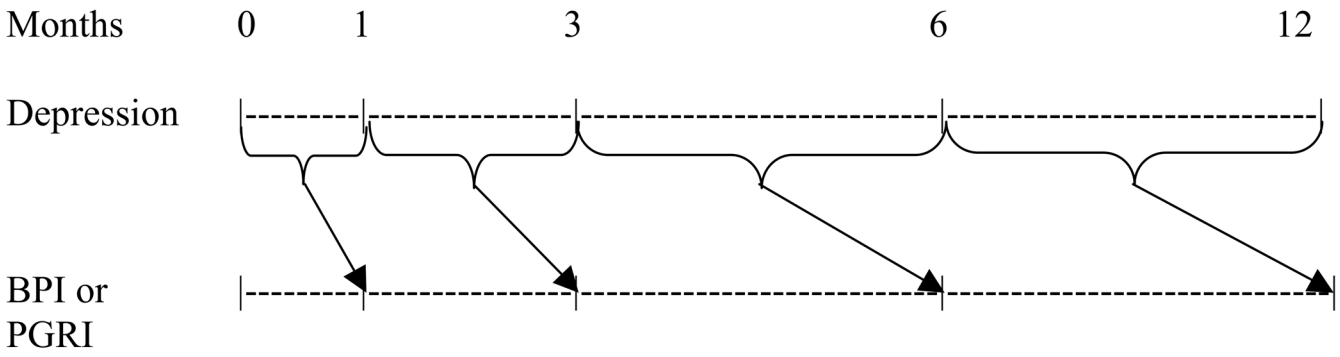

Figure 1.
Repeated measures for examining whether change in depression predicts either Brief Pain Inventory (BPI) severity score or Pain Global Rating of Improvement (PGRI) over 12 months.

Table 1

Baseline Characteristics of Participants with Cancer-Related Pain (T0)

Baseline Characteristics	***N* =274**
	***Mean* (*SD*)**
Age	58.08 (10.54)
SED Index[a]	1.30 (0.98)
Medical Comorbidity (no. of diseases)	2.09 (1.68)
Baseline Cancer-related Pain (BPI severity score, 0–10 scale)	5.22 (1.82)
	n (%)
Group	
Intervention	137 (50.0)
Control	137 (50.0)
Symptom	
Pain	96 (35.0)
Pain and Depression	178 (65.0)
Gender	
Male	93 (33.9)
Female	181 (66.1)
Race	
White	212 (77.4)
Black and others[b]	62 (22.6)
Marital Status	
Married	130 (47.4)
Unmarried	144 (52.6)
Type of Cancer	
Breast	70 (25.6)
Lung	53 (19.3)
Gastrointestinal	51 (18.6)
Lymphoma/Hematological	40 (14.6)
Genitourinary	27 (9.9)
Other	33 (12.0)
Phase of Cancer	
Newly-diagnosed	104 (38.0)
Maintenance or disease-free	110 (40.2)
Recurrent or progressive	60 (21.9)

Note: BPI = Brief Pain Inventory; SED Index = Socioeconomic Disadvantage Index.

[a]The SED Index included variables of education (“less than high school” = 1 point), employment (“unable to work due to health or disability” = 1 point), and income (“not enough” = 1 point).

[b]Other races were only 1.8% (*n* = 5) in this sample.

Table 2

Multivariate Predictors of Cancer-related Pain Improvement over 12 Months

	Outcome Variables					
	BPI Severity Score			Pain Global Rating of Improvement		
	Beta	***t***	***p***	**Odds Ratio**	**95% CI**	***p***
Intervention Group	−.92	−4.68	< **.001**	2.53	1.65–3.89	< **.001**
Baseline Cancer-related Pain	.55	9.84	< **.001**	.90	.80–1.02	.08
Time (Months from Baseline)	−.04	−2.89	**.004**	1.1	1.05–1.14	< **.001**
Predictor Variables[a]						
Improvement in Depression (HSCL-20)[b]	−.31	−2.97	**.003**	1.84	1.35–2.51	< **.001**
SED Index	.25	2.12	**.034**	.73	.56–.94	**.016**
Medical Comorbidity	.20	3.05	**.002**	.84	.73–.96	**.015**
Phase of Cancer			.07			**.014**
Newly-diagnosed vs. Recurrent/progressive	−.43	−1.53		2.12	1.15–3.90	
Maintenance/disease-free vs. Recurrent/progressive	.09	.32		1.11	.61–1.99	

Note: BPI = Brief Pain Inventory; HSCL-20 = Hopkins Symptom Check List-20; SED Index = Socioeconomic Disadvantage Index; CI = Confidence Interval; *p* value < 0.05 is in boldface.

[a] In addition to variables in the table, we also adjusted for age, gender, race, marital status, and type of cancer. None of these variables were significant in the models.

[b] HSLC-20 change scores between 0 month and 1 month (T0–T1), between 1 month and 3 months (T1–T3), between 3 months and 6 months (T3–T6), and between 6 months and 12 months (T6–T12).